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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,769	HEYWOOD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *21-23 and 30-38* is/are withdrawn from consideration.

5)☒ Claim(s) *5-7* is/are allowed.

6)☒ Claim(s) *1-4, 8-20, 24-29 and 39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment filed 27 June 2006 has been entered in full.

Election/Restrictions

2. Applicant's election with traverse of the invention of Group I, claims 1-20, 24-29 and 39-44 in the reply filed on 06 December 2007 is acknowledged. The traversal is on the grounds that the cited prior art of Humphreys et al (Journal of Immunological Methods, 209:193-202, 1997, IDS ref. 11 filed 10/20/2006)does not teach a Fab or Fab' modified by replacement of either the interchain cysteine of CH1 or the interchain cysteine of CL with another amino acid. This is not found persuasive because, while Humphreys et al teaches replacement of the interchain cysteines of CL and CH1 to serines, the prior art cited in the instant Office Action (e.g., Carter et al, see below) does teach a Fab or Fab' modified by replacement of either the interchain cysteine of CH1 or the interchain cysteine of CL with another amino acid. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features, meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. Hence, in view of the cited prior art (e.g., Carter et al, see below) there is no technical relationship left over the prior art among the claimed inventions involving one or more of the same or corresponding special technical features, leaving two or more dependent claims without a single general inventive concept.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 21-23 and 30-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1-20, 24-29 and 39-44 are under consideration.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 20 October 2006 has been fully considered by the examiner. A signed and initialed copy of the IDS is included with the instant Office Action.

Specification

6. It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/GB04/02871, filed July 1, 2004. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35

U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Objections

7. Claim 43 objected to in the recitations "claims 1 or 24", which is grammatically inaccurate and should read claim 1 or 24.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-16 are indefinite in reciting that both the cysteine in the light chain constant region and the cysteine in the heavy chain constant region are attached to an effector molecule. Base claim 1 recites that either the interchain cysteine of the CH1 or the interchain cysteine of the CL is substituted with another amino acid, thus, it is unclear what is contemplated by dependent claim 16 in which the two cysteines are attached to an effector molecule, i.e., are not substituted with another amino acid. As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claims.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 15-16, 20 and 24-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (see MPEP 2163).

In the instant case, the claims are drawn to an antibody fragment comprising a Fab or Fab' fragment that has been modified by attachment of two or more effector molecules to a cysteine in the light chain constant regions and to a cysteine in the heavy chain constant region, wherein the two cysteines would otherwise be linked to each other via a disulfide bond if the effector molecules were not attached, or wherein the heavy chain in the fragment is not covalently bonded to the light chain and an effector molecule is attached to each of the interchain cysteines of CL and CH1, and wherein at least one further effector molecule is attached to a cysteine in the light chain constant region and/or to a cysteine in the heavy chain constant region and wherein the fragment is a Fab' fragment that contains a modified hinge selected from SEQ ID Nos:1-14. Thus, the instant claims encompass a genus antibody fragments comprising a Fab or Fab' wherein the interchain cysteines of the heavy and light chains are not substituted and wherein each of the interchain cysteines are attached to an effector molecule and the heavy and/or light chain further comprises an additional cysteine attached to an effector molecule, however, the written description in the present application only discloses the attachment of an effector molecule to either the interchain cysteine of CL or an engineered cysteine in the light chain constant region, and additional effector molecules are attached elsewhere in a Fab' fragment, in particular the hinge region (see pg. 13). Further, the specification discloses that thiol based reduction typically resulted in monoPEGylated Fab' because the reductants were not strong enough to reduce the inter-chain disulfide bond. The attachment of two or more PEG molecules was accomplished when the inter-chain disulfide linkage between the heavy and light chain was removed by replacing either the interchain cysteine of CL or the interchain cysteine of CH1 with serine (see Example 1).

Thus, the instant disclosure does not provide sufficient written description for antibody fragments comprising a Fab or Fab' comprising two or more effector molecules wherein each interchain cysteine of the CH1 and CL are attached to an effector molecule (e.g., PEG), or wherein the antibody fragment further comprises at least one further effector molecule attached to a cysteine in the light and/or heavy chain. The written description does not set forth a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus of antibody fragments comprising a Fab or Fab' fragment modified by attachment of two or more effector molecules, wherein each interchain cysteine of the CH1 and CL are attached to an effector molecule and the antibody fragments further comprise at least one additional effector molecule in the light chain constant region and/or at least one additional effector molecule in the heavy chain constant region. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. The disclosure of the attachment of additional effector molecules elsewhere in a Fab' fragment, in particular the hinge region, does not adequately convey the genus of antibody fragments comprising a Fab or Fab' wherein each interchain cysteine of the CH1 and CL regions are attached to an effector molecule and the light chain constant region comprises at least one further effector molecule attached to a cysteine in the light chain constant region and the genus is highly variable. Further, the disclosure that thiol based reduction typically resulted in monoPEGylated Fab' because the reductants were not strong enough to reduce the inter-chain disulfide bond and the attachment of two or more PEG molecules when the inter-chain disulfide linkage between the heavy and light chain was removed by replacing either the interchain cysteine of CL or the interchain cysteine of CH1 with serine does not adequately describe the genus of antibody fragments comprising a Fab or Fab' wherein each interchain

cysteine of the CH1 and CL regions are attached to an effector molecule. Clearly, one of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-4, 8-15, 17-18, 39-40 and 42-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter P. J. (WO 93/06217, 4/1/1993) as evidenced by Bodmer et al (WO 89/01974).

Carter teaches Fab and Fab' fragments in which either the cysteine of the heavy chain or the light chain which form the inter-chain (heavy-light) disulfide bond is substituted with serine wherein elimination of the interchain disulfide bond does not result in undesirable levels of dissociation between the heavy and light chains, wherein the Fab' may include a hinge region, a modified hinge having more than one cysteinyl residue or a naturally occurring hinge region such as human IgG1 (necessarily comprises SEQ ID NO:1 as evidenced by Bodmer et al, see Fig. 1), and wherein the free thiols may be attached to a diagnostic or therapeutic agent (i.e., effector molecule) (see entire document, particularly pp. 2, 5, 7-8, 11-12, 15, lines 21-26, pg. 16, lines 4-12, pp. 19-20 and 27). Carter et al also teach host cells comprising the Fab and Fab' fragments in which either the cysteine of the heavy chain or the light chain which form the inter-chain (heavy-light) disulfide bond is substituted with serine as well as pharmaceutical compositions comprising the Fab and Fab' fragments and a pharmaceutically acceptable carrier.

With respect to claim 4, products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Thus, the modified Fab and Fab' fragments in which the heavy chain cysteine that forms a disulfide bond with the light chain (e.g., interchain cysteine of CH1) has been replaced with serine of Carter, identical to the claimed antibody fragment comprising a Fab or Fab' fragment modified by replacement of the interchain cysteine of CH1 with another amino acid and as such, the interchain

cysteine of the CL of the modified Fab and Fab' fragments of Carter would necessarily form a disulfide linkage with a cysteine in the hinge region. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Thus. Carter et al anticipate the claims as evidenced by Bodmer

14. Claims 1-2, 4, 8-15, 17-19 and 39-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06).

Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 (e.g., antibody fragment comprising Fab') fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules or effector molecules, and wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and the PEG or effector molecules are attached via a cysteine residue or residues engineered into the hinge region and/or to the cysteine residue in the light or heavy chain that would ordinarily form the disulfide bridge linking the light and heavy chains and Hesi teaches that the above-described conjugates may comprise two or more of the antibody fragments covalently linked together by PEG, wherein the antibody fragments may be the same or different fragment type and can have the same or different antigen specificity (see entire document, particularly pp. 21-27, 37-38 and 42). Hesi et al also teach host cells for expressing the anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments lacking the disulfide bridge linking the heavy and light chains by substituting the

cysteine residue of the heavy or light chain with serine (see pp. 98-102 as well as pharmaceutical compositions comprising the anti-IL-8 antibody fragments and a pharmaceutically acceptable carrier, excipient or stabilizer (see pp. 104-105).

With respect to claim 4, products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Thus, the modified anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments in which the heavy chain cysteine that forms a disulfide bond with the light chain (e.g., interchain cysteine of CH1) has been replaced with serine of Hesi et al, identical to the claimed antibody fragment comprising a Fab and Fab' fragment modified by replacement of the interchain cysteine of CH1 with another amino acid and as such, the interchain cysteine of the CL of the modified anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments of Hesi would necessarily form a disulfide linkage with a cysteine in the hinge region. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Thus. Hesi et al anticipate the claims.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been

obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) in view of Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06).

Hesi et al have been described supra. Hesi et al do not specifically teach wherein the hinge region comprises any one of the sequences of SEQ ID Nos:1-14. This deficiency is made up for in the teachings of Humphreys.

Humphreys teach Fab' hinge region peptides that efficiently generates dimers (e.g., di-Fab'), which are highly resistant to chemical reduction *in vivo* and the hinge peptides are well tolerated in *E.coli* and are non-immunogenic and the hinge region peptides of Humphreys are identical to the hinge regions of SEQ ID Nos:1-3 (see entire document, particularly pp. 2 and Table II).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced PEGylated anti-IL-8 di-Fab' fragments modified by replacement of either interchain cysteine with serine and comprising the hinge peptides taught by Humphreys for therapeutic benefit of inflammatory disorders.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced anti-IL-8 di-Fab' fragments modified by replacement of either interchain cysteine with serine and comprising the hinge peptides taught by Humphreys for therapeutic benefit of inflammatory disorders in view of Hesi et al and Humphreys because Hesi et al teach PEGylated anti-IL-8 Fab' fragments for the treatment of inflammatory disorders wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and Humphreys teach Fab' hinge region peptides that efficiently generates dimers (e.g., di-Fab), which are highly resistant to chemical reduction *in vivo* and the hinge peptides are well tolerated in *E.coli* and are non-immunogenic and the hinge region peptides of Humphreys are identical to the hinge regions of SEQ ID Nos:1-3. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use the hinge peptides of Humphreys in the PEGylated anti-IL-8 Fab' fragments of Hesi et al for efficient generation of nonimmunogenic di-Fab' fragments in *E.coli* that are resistant to chemical reduction *in vivo*. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 di-Fab' fragments modified by replacement of either interchain cysteine with serine and comprising the hinge peptides of Humphreys for

therapeutic benefit of inflammatory disorders in view of Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 24-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al (Analytical Biochemistry, 304(2):147-156, May 15, 2002) in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) and Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06).

Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and selenol-catalyzed reduction of disulfide bonds in Fab fragments has previously been reported (see entire document, particularly abstract, pp, 148, 154-155 and Fig. 1). Singh et al do not specifically teach an antibody comprising a Fab or Fab' fragment wherein the heavy chain in the fragment is not covalently bonded to the light chain and an effector molecule is attached to each of the interchain cysteines of CL and CH1, and wherein at least one further effector molecule is attached to a cysteine in the light chain constant region and/or to a cysteine in the heavy chain constant region and wherein the fragment is a Fab' fragment that contains a modified hinge selected from SEQ ID Nos:1-14. These deficiencies are made for in the teachings of Hesi et al and Humphreys et al.

Hesi et al have been described supra.

Humphreys have been described supra. Humphreys also teaches that Fab' dimers comprising the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including polyethylene glycol may be attached (e.g., see pg. 9, lines 2-5 and 34)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al for therapeutic benefit of inflammatory disorders.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys because Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules or effector molecules via a cysteine residue or residues engineered into the hinge region and Humphreys teach Fab' hinge region peptides (i.e., SEQ ID Nos:1-3) that efficiently generates dimers (e.g., di-Fab), and the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including polyethylene glycol

may be attached. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising the cysteine containing hinge peptides of SEQ ID Nos:1-3 as taught by Humphreys and reduced using the selenol-catalyzed reduction of interchain disulfides to expose reactive thiols to which PEG molecules are attached since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Singh et al provides evidence that reduction of interchain disulfide bonds of an antibody does not result in a significant decrease in affinity or stability and selenol-catalyzed reduction of disulfide bonds in Fab fragments has been performed previously (Singh et al, pg. 148 1st col.). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1-2, 4, 8-15, 17-19 and 39-44 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06).

Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 are drawn to a Fab or Fab' fragment comprising one polypeptide chain that comprises the amino acid sequence of SEQ ID NO:1 (e.g., TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the Fab or Fab' fragment has one or more effector or reporter molecules attached to it. Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 do not specifically teach wherein either the interchain cysteine of the CH1 or CL is substituted with another amino acid, wherein the amino acid is serine and wherein the interchain cysteine of the CL or CH1 which is not substituted is attached to an effector molecule, wherein the

effector molecules is PEG, a host cell expressing the Fab or Fab' fragment, or pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient. These deficiencies are made up for in the teachings of Hesi et al.

Hesi et al have been described supra.

The claims in the instant application are obvious variants of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce an anti-IL-8 Fab or Fab' comprising the hinge peptide of SEQ ID NO:1, wherein either the interchain cysteine of the CH1 or CL is substituted with serine wherein free thiols of the CH1 or CL and the hinge cysteines of SEQ ID NO:1 are attached to PEG, and a host cell expressing the Fab or Fab' fragment, as well as pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient for the treatment of inflammatory disorders.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce an anti-IL-8 Fab or Fab' comprising the hinge peptide of SEQ ID NO:1, wherein either the interchain cysteine of the CH1 or CL is substituted with serine wherein free thiols of the CH1 or CL and the hinge cysteines of SEQ ID NO:1 are attached to PEG, and a host cell expressing the Fab or Fab' fragment, as well as pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient for the treatment of inflammatory disorders in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Hesi et al. Therefore, one of ordinary skill in the art would have been motivated to modify the Fab or Fab' fragments of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 for the attachment of the PEG molecules to the free thiol of the CH1 or CL in addition to the thiols in the hinge peptide of SEQ ID NO:1 since PEGylation has the potential to increase residence time and reduce immunogenicity in vivo according to Hesi et al (see pg. 1) and IL-8 antibodies

provide a therapeutic benefit in patients suffering from inflammatory disorders. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce an anti-IL-8 Fab or Fab' comprising the hinge peptide of SEQ ID NO:1, wherein either the interchain cysteine of the CH1 or CL is substituted with serine wherein free thiols of the CH1 or CL and the hinge cysteines of SEQ ID NO:1 are attached to PEG, and a host cell expressing the Fab or Fab' fragment, as well as pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient for the treatment of inflammatory disorders in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Hesi et l.

Claims 1-2, 4, 8-15, 17-19 and 39-44 are directed to an invention not patentably distinct from claims 7 and 10 of commonly assigned U.S. Patent No. 6,642,356 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,642,356 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

20. Claims 5-7 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643